

Amendment and Response

Serial No.: 09/438,206

Confirmation No.: 9018

Filed: 12 November 1999

For: METHODS AND COMPOSITIONS FOR TREATING MAMMALIAN SPINAL CORD INJURIES

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D2 38. (Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord after the injury but within a period no greater than about 24 hours after said injury with polyethylene glycol in an amount effective to restore nerve impulse conduction [increase a compound action potential in] through said injured spinal cord.

D3 44. (New) The method according to claim 22 or 38 wherein the restoration of nerve impulse conduction is evidenced by a detectable increase in conduction action potentials, observation of anatomical continuity, restoration of more than one spinal root level, or an increase in reflex behavior

REMARKS

Claims 22 and 38 having been amended, and claim 44 having been added, claims 22-30, 38-40, 43 and 44 are pending. Support for the amendments to claims 22 and 38 reciting a restoration of nerve impulse conduction through the spinal cord, is found in the specification at, for example, page 1, lines 22-31 and page 14, lines 25-26. Support for newly added claim 44 is found, for example, in the specification at page 14, lines 27-29 (increase in compound action potentials); page 15, lines 2-6 (observation of anatomical continuity); page 15, lines 6-11 (restoration of more than one spinal root level); and page 15, lines 11-19 (increase in reflex behavior).

Examiner Interview Summary

The Examiner is thanked for the telephone interview granted to Applicants' Representative Victoria Sandberg and Applicant Dr. Richard Borgens on October 29, 2002. All pending claims were discussed. The discussion focused on the applicability of the Davis et al. reference as prior art to the pending claims, and specifically whether spinal cord injury accompanies disc surgery. In an effort to distinguish Davis et al., and to facilitate allowance of the pending claims, Applicants agreed to present additional evidence that (1) no spinal cord

injury occurs during a properly performed disc surgery, and further that (2) the outcome of successful disc surgery (i.e., reduction in nerve impulses) is essentially the opposite of the outcome of successful of spinal cord injury (i.e., restoration of nerve impulses).

Second Request for Entry of Previously Filed Amendment under 37 C.F.R. §1.116

In the Request for Continued Examination (RCE) mailed May 23, 2002, Applicants requested entry of the Amendment under 37 C.F.R. §1.116 filed on February 22, 2002, as well as a subsequent Amendment submitted with the Request. A copy of the Request for is attached as Exhibit A. Although the Examiner entered the Amendment filed with the Request (Box 1.b.i. of the Request form), it appears the request for entry of the after-final Amendment (Box 1.a.i. on the Request form) may have been overlooked. Entry of the Amendment under 37 C.F.R. §1.116 filed on February 22, 2002, is again respectfully requested.

Applicants note that marked-up copies of the Amendment submitted with the RCE (mailed May 23, 2002) and the Amendment under 37 C.F.R. §1.116 (mailed February 22, 2002), can be found in the Appendix A transmitted with each of those communications.

Rejections under 35 U.S.C. §112, First and Second Paragraphs

Claims 30-37 stand rejected under 35 U.S.C. §112, first paragraph. Claims 22-43 stand rejected under 35 U.S.C. §112, second paragraph. These rejections are respectfully traversed.

Entry of the Amendment after Final mailed February 22, 2002, has been requested. As a result, claims 31-37, 41 and 42 are canceled, without prejudice, thereby rendering the rejections moot with respect to those claims.

Of the rejected claims, only claims 22-30, 38-40 and 43 remain pending. Applicants fully incorporate herein the comments made in the Amendment mailed February 22, 2002, and direct the Examiner's attention thereto. For the Examiner's convenience, a copy of the Amendment mailed February 22, 2002, is included herewith as Exhibit B.

Moreover, claims 22 and 38 have been further amended herewith to delete recitation of "compound action potential," thereby rendering moot the Examiner's rejection of these claims under 35 U.S.C. §112, second paragraph, for indefiniteness.

Reconsideration and withdrawal of the rejection of claims 30-37 under 35 U.S.C. §112, first paragraph, and claims 22-43 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. §102(b)

Claims 22, 24-29, and 38-39 remain rejected under 35 U.S.C. §102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306). This rejection is respectfully traversed.

Davis et al. describe surgeries for symptomatic unilateral disc protrusion at either L4-5 or L5-S1. The surgeries were accompanied by intraoperative epidural application of methylprednisolone acetate (MP) in a solution containing 28 mg/mL polyethylene glycol (PEG) to increase solubility.

Claim 22, as amended, reads as follows:

22. A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord after the injury but within a period no greater than about 24 hours after said injury with a C₁-C₁₀ polyalkylene glycol in an amount effective to restore nerve impulse conduction through said injured spinal cord.

It will be appreciated that claim 22 has been amended to delete recitation of a relative increase in "compound action potential" and an increase in "behavioral recovery"; in their place, claim 22 recites a restoration of "nerve impulse conduction through said injured spinal cord." Similar amendment has been made to claim 38. A spinal cord injury results in a loss in nerve impulse conduction along the spinal cord (specification at page 1, lines 22-32). This amendment is intended to clarify that contacting the spinal cord with a C₁-C₁₀ polyalkylene glycol under the

recited conditions causes a restoration in nerve impulse activity. Such restoration in nerve impulse activity can be detected in a variety of ways, such as detection of an increase in conduction action potentials (specification at page 14, lines 27-29), observation of anatomical continuity (specification at page 15, lines 2-6), restoration of more than one spinal root level (specification at page 15, lines 6-11), and/or behavioral analysis (such as increase in reflex behavior) (specification at page 15, lines 11-19). Newly added claim 44 recites a restoration of nerve impulse conduction that is evidenced by any of these changes.

The claims remain directed to treatment of "an injured spinal cord." In the Office Action mailed August 15, 2002, the Examiner stated that Davis et al. teaches a spinal cord injury because "patients undergoing disc excision surgery would have, at least, a slight contusion or compression to their spinal cord; or, alternatively, patients with disc herniation, needing disc excision, because their spinal cord is compressed."

Applicants respectfully, but vigorously, disagree; Davis et al. does *not* teach an injured spinal cord. Disc surgery (discectomy), when properly performed, is not accompanied by, nor does it cause, spinal cord injury. Likewise, persons suffering from a spinal cord injury are not treated using discectomy. In further support of Applicants' reading of Davis et al., Applicants submit the Declaration under 37 C.F.R. §1.132 of Dr. Scott Shapiro, a distinguished practicing neurosurgeon at the University of Indiana Medical School. The Declaration of Dr. Shapiro, and the surgical textbook cited therein, actually *teach away* from injury of the spinal cord during disc surgery, as spinal cord injury is to be strictly avoided.

Applicant further notes that claims 22 and 38, as amended herewith, recite the restoration of nerve impulse conduction through the injured spinal cord. In the Office Action mailed August 15, 2002, the Examiner states that the disc treatment of Davis et al. which reduces pain and spasm "indicates that the patients' behavioral and neural functions are restored." Applicants strongly disagree. The important point here is that in a spinal cord injury, transmission of nerve impulses through the spinal cord is *blocked*. Successful treatment restores the movement of those nerve impulses. A sensation of pain after surgical treatment of a spinal cord injury would, if anything, represent a successful surgery!

Pain and spasm associated with disc injury, on the other hand, result from excessive amounts (not reduced amounts) of nerve impulse activity. A reduction in pain and spasm does *not*, as suggested by the Examiner, indicate a "restoration" of nerve function. To the contrary, disc surgery is successful when the nerve impulses through the nervous system have, if anything, been *reduced or dampened*, as evidenced by reduced pain and/or spasms.

Reconsideration and withdrawal of the rejection of claims 22, 24-29, and 38-39 under 35 U.S.C. §102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306), is respectfully requested. If, after consideration of the Applicants' arguments and review of Dr. Shapiro's Declaration, the Examiner continues to maintain this rejection, Applicants respectfully request that the Examiner accompany the rejection with documentary evidence and/or an Affidavit of personal knowledge to support the Examiner's conclusion that discectomy patients have suffered spinal cord injuries. MPEP 2144.03.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 23, 30-37, and 40-43 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306) in view of Potter et al. (Clin Invest Med, 19(4), Suppl.: S80 #533). This rejection is respectfully traversed. Of the rejected claims, only claims 23, 30, 40 and 43 remain pending.

For reasons stated above, Applicants submit that the primary reference, Davis et al., while it does teach incidental application of a polyethylene glycol during lumbar disc surgery, does not teach treatment of an injured spinal cord. To the contrary, during lumbar disc surgery, injury to the spinal cord is to be strictly avoided (see the Declaration of Dr. Scott Shapiro). As a consequence, it is respectfully submitted that pending claims 23, 30, 40 and 43, directed to treatment of an injured spinal cord, are not rendered obvious over Davis et al. (Journal of Spinal Disorders, 1990;3(4):299-306) in view of Potter et al. (Clin Invest Med, 19(4), Suppl.: S80 #533).

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Summary

It is respectfully submitted that the pending claims 22-30, 38-40, 43 and 44 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be in any way assisted or expedited thereby.

Respectfully submitted for
Shi et al.

By
Muetting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813



26813

PATENT TRADEMARK OFFICE

By: _____

Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612)305-1226

Date

14 November 2002

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By: _____

Name: JACQUELYN K. TORBERG



**APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE**

**Serial No.: 09/438,206
Docket No.: 290.0042 0101**

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Claims

For convenience, all pending claims are shown below.

22. (Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord after the injury but within a period no greater than about 24 hours after said injury with a C₁-C₁₀ polyalkylene glycol in an amount effective to restore nerve impulse conduction [increase a compound action potential in] through said injured spinal cord [relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated].
23. The method according to claim 22 wherein said spinal cord is severed.
24. The method according to claim 22 wherein said spinal cord is crushed spinal cord.
25. The method according to claim 22 wherein said polyalkylene glycol is selected from the group consisting of polymethylene glycol, polyethylene glycol, polypropylene glycol, polybutylene glycol, polypentylene glycol, polyhexylene glycol, polyheptylene glycol, polyoctylene glycol, polynonylene glycol, polydecylene glycol and mixtures, thereof.
26. The method according to claim 25 wherein said polyalkylene glycol is administered to said patient in a pharmaceutically acceptable carrier.

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27. The method according to claim 26 wherein said polyalkylene glycol is selected from the group consisting of polyethylene glycol, polypropylene glycol and mixtures thereof.
28. The method according to claim 22 wherein said polyalkylene glycol is polyethylene glycol.
29. The method according to claim 26 wherein said polyalkylene glycol is polyethylene glycol having a molecular weight ranging from about 40 daltons to about 3500 daltons.
30. The method according to claim 22, wherein said polyalkylene glycol is polyethylene glycol and wherein said method further comprises the step of contacting said injured spinal cord with a potassium channel blocker in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient.
38. (Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord after the injury but within a period no greater than about 24 hours after said injury with polyethylene glycol in an amount effective to restore nerve impulse conduction [increase a compound action potential in] through said injured spinal cord [relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated].
39. The method according to claim 38 wherein said polyethylene glycol has a molecular weight ranging from about 40 daltons to about 3500 daltons.

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40. The method according to claim 38 further comprising the step of contacting said injured spinal cord with a potassium channel blocker in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol.
43. The method according to claim 40 wherein said polyethylene glycol has a molecular weight ranging from about 40 daltons to about 3500 daltons.
44. (New) The method according to claim 22 or 38 wherein the restoration of nerve impulse conduction is evidenced by a detectable increase in conduction action potentials, observation of anatomical continuity, restoration of more than one spinal root level, or an increase in reflex behavior.